2:30-4:00 Beyond Genome Plenary Session

Top Ten Opportunities in the Post-Genome Era

(Please see page 5 for details)

4:00-5:00 Refreshment Break with Poster and Exhibit Viewing

MODELING SIGNALING PATHWAYS

5:00-5:30 **From Critical Pathway Identification to a Computational Model and its Application to Biomarker Identification**

Dr. Ulrik Nielsen, Vice President of Research, Merrimack Pharmaceuticals

At the example of the IGF1-R and ErbB signaling pathways we will discuss the crosstalk between two very similar GF pathways. Based on a computational model of the IGF1/2-R and ErbB signaling we will present the application of such a combined model for the identification of Biomarkers.

5:30-6:00 **RepairCHIP: A New Platform to Explore the Activated Pathways in Cancer**

Dr. Jan Feng, Associate Professor, Chemistry, Temple University

RepairCHIP is an oligonucleotide microarray that contains genes corresponding to the proteins of RepairNET, a cellular network of more than 1200 proteins associated with the DNA damage response. By measuring the gene expression profiles in cancer, we can investigate how cancer stimulating signals evade the regulatory controls of the DNA damage response. We have developed RepairPATH, a pathway-exploration algorithm that identifies the activated signaling pathways in cancer by incorporating the data from measured gene expression profiles with the knowledge of functional relationship between the proteins in RepairNET.

6:00-6:30 **The Current Model of the NF-kappaB Pathway: Theory Entwined with Experiments**

Dr. Andre Levchenko, Assistant Professor, Biomedical Engineering, Johns Hopkins University

The presentation will describe the continued development and experimental validation of the model of the NF-kappaB mediated signal transduction in response to multiple stimuli. The in-depth review of our recent experiments with microfluidic chips leading to a detailed experimental view of the pathway activation will be presented. Finally, how the model can be instrumental in our understanding of the innate immune response will also be discussed.

6:30 Close of Day

Wednesday, June 21

8:00am Registration

8:30-10:00 Breakfast Roundtable Discussions

Top Ten Opportunities in the Post-Genome Era

(Please see page 5 for details)

10:00-11:00 Coffee Break with Poster and Exhibit Viewing

MODELING PATHWAY MODULATION BY DRUGS

11:00-11:30 **Predictive Integrative Biology and Downstream Experimental Testing: A Synergistic Paradigm that Deciphers Complex Pathological Processes and Modes of Drug Action**

Dr. Francois Iris, President & CSO, Bio-Modeling Systems

Knowing the potential targets of a drug together with their functions is not synonymous with having knowledge of the physiological mechanisms that must be affected and the way in which they must be affected to have a successfully therapeutic impact. To gain the necessary functional knowledge, widely disseminated information, under a large variety of forms and accession formats, must be integrated to create coherent and pertinent predictive biological models that can then be directly implemented in the context of the pathological problem being addressed. A set of validated, computer-driven solutions to these problems has been developed and, to date, ten such predictive models of complex human pathologies / biological processes have been produced. Four have been experimentally tested, all four validated, two have been published (NAR & J. Mol. Endocrinol.) and the other two are being made ready for publication. Two examples will be exposed in detail: the as yet poorly understood pathological mechanisms leading to vacuolation and neuronal death in Creutzfeld-Jakob Disease and the unknown mode of action of a peptide observed to induce dormancy in aggressively malignant epithelial cells both *in vivo* and *in vitro*.

11:30-12:00 **The Generation and Use of Regulatory Gene Networks in Endothelial Cells**

TBA

Endothelial cells play a key role in the regulation of physiological processes that are implicated in significant pathologies including cardiovascular disease, cancer and numerous conditions where inflammation occurs. In order to understand the regulatory mechanisms operating in these cells we have developed methods to generate regulatory gene networks that are not based on pre-existing knowledge but are built by inferring gene-to-gene regulatory relationships from hundreds of new expression array experiments. We have used several hundred different siRNA-mediated gene knock-downs and combined these data with those obtained from time-course expression profiles. For any proposed gene-to-gene relationship we have hundreds of independent data points and thus the method is robust to the occasional outlier. Using a Bayesian statistical and computationally intensive procedure, we have generated networks that reveal known and novel regulatory relationships. Our networks correctly identify numerous previously identified NF-kappa B1 target genes; however, they also reveal other targets downstream of TNF-alpha, including new NF-kappa B1 regulated genes. This approach is also effective in elu cidation of the mechanism of action of both known and unknown drugs.

12:00-12:30 **Pathway Informatics Environment for Modeling Drug Responses**

Mr. Ilya Mazo, President, Ariadne Genomics

Correct interpretation of gene expression and proteomics data is crucial for identifying good biomarkers and predicting side effects in toxicology studies. We favor the analysis of regulatory network motifs as a viable alternative to correlation analysis that tends to overlook complex associations and to system-wide modeling approaches that depend on the amounts of data not easily available as of today. Our analytic software can systematically mine the database of 500,000+ functional relationships extracted from literature for small network motifs that are robust in regard to the effects induced at the gene or protein expression levels; we have used the library of such motifs to improve the prioritization of biomarker sets in several real life studies.

12:30-2:00 Lunch on Your Own

UNDERSTANDING CANCER MECHANISM FROM EXPRESSION DATA

2:00-2:30 **Uveal Melanoma: Molecular Networks Underlying Extracellular Matrix Reorganization and Tumor Progression**

Dr. Zarema Arbieva, Assistant Professor & Director, Medicine, The University of Illinois at Chicago

An *in vitro* uveal melanoma model confirms the critical involvement of extracellular matrix in facilitating tumor progression. Molecular interaction networks underlying such progression are identified by means of novel statistical analysis of differential transcriptional profiles. The analysis is performed based on proprietary database of molecular interactions (Ariadne Genomics, Inc.). The relevance of suggested molecular interactions is confirmed by ample experimental and clinical evidence.

2:30-3:00 **A Putative Signature of Chromosomal Instability Inferred from Gene-Expression**

Dr. Zoltan Szallasi, Senior Research Scientist, CHIP, Children's Hospital Boston

We have developed a computational method to identify chromosomal regions with significant localized aberrations in coordinate gene-expression activity and show that the resulting profiles of 'functional aneuploidy' could be used to classify tumors with respect to outcome. Furthermore, a derivative univariate measure of total genomic imbalance was significantly associated with clinical outcome in several cohorts of lung and breast cancer patients. A gene-expression signature of genomic imbalance was highly predictive of clinical outcome in six publicly available datasets representing four solid-tumor types, and was significantly associated with the outcome in several additional cohorts representing two additional types of human tumors. This signature represents the most accurate and most broadly applicable signature of cancer prognosis so far.

3:00-3:30 **Copy Number Variation in Normal Biology and Human Disease and the Need for Sub-Kb Resolution Array CGH**

Dr. Peggy S. Eis, Director, Array CGH Business Unit, NimbleGen Systems Inc

Recent discovery of megabase-sized copy number variants (CNVs) in the human genome has opened a window into the role of genome variation beyond the single nucleotide polymorphism (SNP). Recent studies now indicate that CNVs are numerous, vary in size from Mb down to sub-Kb, and frequently overlap with genes. Some CNVs occur with high frequency in the population, thus contributing to normal genetic variation, while other more rare CNVs are anticipated to play a role in disease, either alone or in combination with other CNVs or genomic mechanisms of regulation (e.g., methylation). In order to investigate the full range of variation in the human genome, we have developed an ultra-high resolution array CGH platform with tunable resolution that enables detection of deletions and amplifications of DNA either genome-wide or in targeted regions with sub-Kb resolution. This technology is being used to study complex diseases such as cancer and will likely become a component of disease association studies.

3:30-4:00 Refreshment Break with Poster and Exhibit Viewing *(Last Chance to View)*

CANCER DISEASE MODELING

4:00-4:30 **A Case Study for Integration Informatics: From Data Integration and Management to Marker-Based Diagnostics Models**

Mr. Robert Stanley, Vice President, Chief Technology Officer, IO Informatics

This case study describes how distributed experimental data is transformed into systems biology pathways for disease modeling in a systems biology environment. The project is taking place under a NIST Advanced Technology Program (ATP) grant involving a partnership between IO Informatics and Icoria (division of Clinical Data, Inc.). Integration, management, query and representation of data and knowledge from internal and external sources, will be described, across levels of granularity - from molecular level data (e.g. genomics, proteomics, metabolomics); through organelles; (e.g. microscopy, fMRI); and organisms (e.g. case, clinical data); to systems models suitable for multi-method screening.

4:30-5:00 **The Obsolescence of Reductionist Biology, Systems Biology Modeling and Cancer Cachexia Therapy Development Based on Emergent Patterns of Organization Rather than on Genes and Molecules**

Dr. Fredric Young, Chief Scientist, Biophysics, Vicus Therapeutics, LLC

Vicus has developed a hierarchical network (HiNET) model of emergent patterns of organization based on principles of self-organized criticality, phase-transitions, integral control and reaction blocks. We will describe our HiNET model of cancer cachexia, a catastrophic wasting disorder secondary to advanced cancer, and its predicted EKG-based biomarkers and reaction-block drug targets. We will show data from our retrospective and prospective VT-122 clinical trials and contrast our clinical results with previous failed attempts targeting specific dysregulated pathways and proteins.

5:00-5:30 **Calibrating Xenografts: Developing Virtual Tumors for Reduced Attrition**

Dr. Maciej Swat, Senior Simulation Scientist, Physiomics plc

As 95% of clinical cancer projects fail, xenografts are a poor predictive tool. Physiomics has a detailed dynamic cell cycle model, for example of aurora kinase inhibition coupled to biomarkers, and has shown that these can explain cell culture responses to drugs. By using autonomous software agents, this is being extended towards a realistic virtual tumor to enable calibration of xenograft data.

5:30 Close of Conference